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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,654	02/14/2002	Charles Andrianjara	A0000477-01-CFP	1864

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/075,654	Andrianjara et al.
Examiner	**Art Unit**
Deepak Rao	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 14, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-41* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 2
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-41 are pending in this application.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of arthritis diseases, does not reasonably provide enablement for treating all diseases mediated by MMP-13 e.g., all types of cancers, etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to 'a method for treating a disease involving a therapy of inhibition of MMP-13 .....' and the specification provides that these diseases include multiple sclerosis, asthma, cancer etc. see page 2 lines 3-9. First, the method of treating covers 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The recitation of 'disease' covers any disease or disorder related to body or mind, and thereby does not limit to the specific diseases which are disclosed in the specification and/or claims. The instant claim language covers diseases that are very difficult to treat, e.g., cancer, multiple sclerosis, etc. and diseases that are yet to be discovered, for which

there is no enablement provided. Even the list of conditions recited in the dependent claims is overly broad because these recite many more diverse, generic disease groups such as inflammatory, dermatological, autoimmune, etc. Substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or "not provided", see *Ex parte Jovanovics*, 211 USPQ 907, 909.

The state of the art also presents the difficulties in identifying selective matrix metalloproteinase inhibitors, see Montana et al. (cited in IDS), "Although individual or combinations of MMPs have been implicated in specific diseases, it has proved a **significant challenge** for medicinal chemists to provide 'selective' inhibitors of these enzymes, targeted at a particular disease" (see page 353, col. 2). Montana et al., further substantiate regarding one class of compounds that "the pharmacokinetics and efficacy of this series of compounds have **not** been reported" (see page 359, col. 1) and conclude with remarks emphasizing the importance of identifying 'selective MMP inhibitors'. The authors further submit that many of the inhibitors are "either in the clinic or in advanced preclinical studies" (see page 359, col. 2), thereby providing that the exact therapeutic action of the inhibitors is yet to be determined. Chen et al. (cited in IDS), also remarked that "Further studies are underway to reach the combined target of selectivity with oral activity" (see page 9654).

The activity for the claimed compounds disclosed in the specification is as metalloproteinase inhibitors, useful to treat various diseases, which include arthritis, multiple sclerosis, cancers, etc. Biological assays are provided in the specification at pages 62-63 and IC_{50}

values for the representative exemplified compounds of formula (I) are provided in Table 1, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders embraced the instant claims. Many of the claimed disorders, e.g., cancer, etc., have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the claimed compounds can treat the different types of diseases recited in the claim having diverse mechanisms.

Claim 38 specifically recites 'a method of treating a disease .... selected from ... cancers' - no compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. In reference to tumor growth and metastasis, Morris et al. (Invasion Metastasis, 1997) stated that "initial arrest and extravasation may be difficult to prevent" (see the PubMed Abstract enclosed). Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use in treating a diverse list of diseases.

2) The state of the prior art: There are no known single group of compounds of similar structure which have been demonstrated to treat the wide variety of diseases instantly recited.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Rasmussen et al., in a recent article (Pharmacol. Ther., Vol. 75, 1997) stated that "Randomized clinical trials, in particular in earlier-stage disease, are required in order to fully characterize the therapeutic potential of this class of agents", see page 74, col. 1. Also, Chambers et al., in their review article (J. National Cancer Inst., Vol. 89, 1997) expressed that "Details of the mechanisms by which MMPs and their

inhibitors contribute to creating an environment that favors the initiation and continued growth of primary and metastatic tumors remain to be elucidated, but are of key importance in cancer therapy". Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits.

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present to direct one to protect a potential host from the disorders nor there are doses given for the treatment of the disorders commensurate in scope with the claims.

6) The breadth of the claims: The instant claims generally embrace treatment of all types of diseases that involve MMP-13 inhibition.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In claim 1, line 2, following 'A compound selected from those of formula (I):', the recitation "The invention relates to cyclized quinazolines of formula (I)" is redundant. The claim appears to be in better form without the recitation of line 2 and therefore, deletion of line 2 is suggested.

2. In the claims, it is recited that "A compound ..... **optionally**, its racemic form**s**, isomer**s** thereof, ... **and** its pharmaceutically acceptable salt**s** thereof". First, the term 'optionally' is redundant and further, the claim reads better if "and" is replaced by -- or --. Also, the plurality of the terms, e.g., "form**s**" is not in proper Markush language, replacing with singular terms, i.e., --form-- and --salt-- is suggested.

3. In the claims, it is recited "isomers thereof" (see claim 1, page 68, line 11), however, it is not clear what type of 'isomers' are intended here. The term represents any type including 'structural' or 'positional' isomers which are made differently and not supported by the disclosed structural formula. The specification does not provide any explanation of the term.

4. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" or "**preferably**" (all occurrences) and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites:

(a) the broad recitation "5 to 10", and the claim also recites "5 to 6" which is the narrower statement of the range/limitation (see page 68, line 15);

(b) the broad recitation "3 to 10", and the claim also recites "3 to 6" which is the narrower statement of the range/limitation (see page 68, lines 19-20);

(c) the broad recitation "1 to 6", and the claim also recites "1 to 4" which is the narrower statement of the range/limitation (see page 68, lines 24-25);

(d) the broad recitation "5 to 10", and the claim also recites "5 to 6" which is the narrower statement of the range/limitation (see page 68, line 25); and

(e) the broad recitation "1 to 6", and the claim also recites "1 to 4" which is the narrower statement of the range/limitation (see page 68, lines 27-28).

5. In claim 1, page 68, line 18, the term "remplaced" is not clear. It appears that this may be a typographical error for -- **replaced** --. Appropriate correction would obviate the rejection.

6. In the claims (see e.g., claim 1, page 68, line 11), the term "N-oxydes" (all occurrences) appears to be a typographical error for -- **N-oxides** --. Appropriate correction in all occurrences is suggested.

7. Claims 24 and 25 are independent claims and for the definitions of the variables W, X, etc., it is recited "as defined above" (see claim 24, page 87, line 2) or "as defined hereinbefore" (see claim 24, page 87, line 13). A claim must contain all limitations within the claim or should refer to another claim having those limitations.

8. Claims 32-36 provide for the use of the compound, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

9. In claims 37 and 38, the term "complaint" is not a proper term following the preamble 'a method of treating'. The claim reads in better form without the term. Further, claim 37 does not recite -- in need thereof -- following the term 'patient'. Without the proper recitation, the claim appears to recite treating any patient whether or not that requires

such treatment. Also, claim 38 recites "....a disease .... selected from .... and **cancers**" wherein the plural form for the term 'cancers' is not consistent with the recitation of 'a disease'.

Claim Rejections - 35 U.S.C. § 101

Claims 32-36 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-20 and 31-41 are rejected under 35 U.S.C. 102(e) as being anticipated by Andrianjara et al., U.S. Patent Application Publication 2003/0078276 (filed February 13, 2002).

The instantly claimed compounds read on the reference disclosed compounds, see the compounds listed in Table V, starting in pages 59-62. The instantly claimed processes of claims 19 and 20 are disclosed in Synthesis Examples 55-56 and 57-61 respectively. The compounds are disclosed to be inhibitors of MMP-13, see page 58, col. 2, paragraph [0306], and are therefore useful for treating e.g., arthritis, see the abstract.

Applicant's claim for domestic priority under 35 U.S.C. 119(e) based on application No. 60/268,757 filed February 14, 2001 is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for the claims of this application. Particularly, the provisional application does not define R_4 to be $-NO_2$, $-SCF_3$, $-OCF_3$, $-SR_5$, $-SOR_5$, etc. Also, the definition of R_3 in the instant claims is not consistent with the definition provided in the provisional application, see for example, the provisional application does not recite 'the group $(R_{13})_q$-B-$(Z_2)_p$-' as part of the R_3 definition.

Receipt is acknowledged of the Information Disclosure Statement filed on May 28, 2002 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (703) 305-1879. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (703) 308-4716. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Deepak Rao
Primary Examiner
Art Unit 1624

May 20, 2003